	1988	1993
Order standardization		
Tests per patients	56.3	41.9
Charge patient	2866	2062
1993 saving $1,163,488		
Same day extubation	1%	50%
Reintubation	0.7%	0%
First day ICU transfer	2%	62%
Six day hospital stay	4.6%	50%
Charges (normalized 1993 dollars)		
106	$46,311	$37,615
107	$34,638	$29,545
Mortality 106/107	3.2	2.7
Number cases	861	795

Systems analysis approach may have a significant impact on resource consumption, changes and length of stay in a clinical setting.

1032-118 Inoue Mitral Valvuloplasty: Profile and Correlates of Hospital Cost

Nowa Omoigui, John Elliott, John Allen, Kim Brown, Mark Hanson, Kingsley Annan, Brian Griffin, Patrick Whitlow, Murat Tuzcu. *The Cleveland Clinic Foundation, Cleveland, OH*

Between January 1992 and December 1993, 46 Inoue Mitral Commissurotomies (IMV) were performed as part of a Multicenter Investigation. In the same period, 19 IMV-eligible open mitral valvuloplasties (OMV) were performed for mitral stenosis. There were no differences in baseline characteristics (p = NS):

	Age (mean)	Female	Echo score (mean)	Valve area (mean)
IMV	51.4 ± 12.01	87.0%	7.1 ± 1.5	1.1 cm^2
OMV	53.6 ± 12.9	94.7%	7.7 ± 2.5	1.1 cm^2

93.5% of IMV were successful without valve surgery. Median costs (in 1993 dollars) using the Transition Systems Inc. accounting method, and length of stay (LOS) were higher for OMV than IMV (p < 0.001). Deaths and Strokes were similar:

	Death	Stroke	LOS (days)	Cost ($)
IMV	2.2%	0.0%	1	5,210
OMV	5.3%	0.0%	7	19,692

Correlates of IMV cost in multivariable stepwise regression analysis were:

Mitral valve replacement	p = 0.0001
Hospital delay >24 hours prior to IMV	p = 0.0035
Final trans-mitral gradient	p = 0.0263

After controlling for LOS, intra-procedural transesophageal echocardiography predicted higher cost (p = 0.006).

In conclusion, IMV is an effective short-stay cost minimizing strategy in appropriate patients. Cost savings can be obtained by expeditiously achieving a low residual gradient while avoiding mitral valve replacement. The cost-benefit of routine transesophageal echocardiography requires further study.

1032-119 What Price CABG? Individual Patient Characteristics that Influence Direct Costs

Timothy A. Denton, George A. Diamond, Jack M. Matloff. *Cedars-Sinai Medical Center, Los Angeles, California*

There are two methods to control procedural costs: (1) make systematic changes that reduce costs on all patients, and (2) identify potentially high cost patients and proactively intervene to keep costs low in those individuals. To determine which patient characteristics are predictive of high cost, we studied a series of 722 consecutive patients (3/12/90 to 3/22/94) undergoing routine CABG (DRG 107 — CABG without catheterization) to determine which individual characteristics contributed to direct costs.

Using the Cedars-Sinai Cardiothoracic Surgery database, we identified 31 prospectively collected candidate variables from the preoperative and operative periods which might contribute to the overall direct costs of bypass. Total direct costs were obtained from the hospital central financial system for each patient. Only patients who survived to discharge were included in the analysis. Forward, stepwise, multiple linear regression was used to determine which candidate variables contributed to total direct costs.

Of the 31 candidate variables, 3 demographic (age, non-private patient, widow(er)), 4 preoperative clinical (presence of symptoms, angina CHA class, CHF NYHA class, peripheral vascular disease), and 1 intraoperative variable (non-use of the internal thoracic artery — ITA) contributed to the cost of CABG (p < 0.04). The following table presents each characteristic and the incremental associated cost of that characteristic:

Peripheral vascular disease	$6,381	Age (cost per decade)	$1,950
Non-private patient	$5,283	CHF NYHA class	$293
Widow(er)	$4,908	Angina CHA class	$195
Non-use ITA	$4,842	Symptomatic	$88

Conclusion: High direct cost patients can be identified prior to a CABG. Although these variables themselves are not directly amenable to modification, proactive intervention through general case management may decrease the total costs of the procedure and allow more efficient allocation of resources. In addition, these data can be directly employed to adjust contract pricing for case-mix.

803 Restenosis: Molecular Mechanisms

Wednesday, March 22, 1995, 4:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Room 9

4:00

803-1 Osteonectin and Osteocalcin mRNA are Expressed in Human Atherosclerotic Lesions and Upregulated Following Balloon Angioplasty

Sanjay Srivasta, Robert Schwartz, William Edwards, Lorraine Fitzpatrick. *Mayo Clinic, Rochester, MN*

Matrix proteins such as osteonectin and osteocalcin play an active role in mineralization, cell adhesion and migration. Osteocalcin is chemoattractive for monocytes and mesenchymal cells; its synthesis is vitamin K-dependent and it is associated with mineralization. Osteonectin binds to calcium and is abundant in platelets and remodeling tissue. We studied the expression of ON and OC mRNA in coronary arteries obtained at autopsy in patients who underwent balloon angioplasty (PTCA). Primary atherosclerotic and PTCA sections were hybridized with ^{35}S-labelled oligonucleotides derived from sense and antisense sequences. Sense controls were negative and signal was rarely detected in segments without atherosclerosis. In arteries that had PTCA performed, abundant signal was found in the organizing thrombus and in the adventitia, with increased abundance of mRNA detected over time after PTCA. In uninjured segments of atherosclerotic artery, OC and ON were detected in the plaque and extensively throughout the adventitia and associated with calcified areas. We suggest: 1) Expression of OC and ON mRNA occurs in human atherosclerotic arteries and is associated with calcification; 2) OC and ON mRNA expression is not confined to plaque and is present extensively in the adventitia; 3) Following PTCA, upregulation of OC and ON mRNA in the adventitia may regulate the reparative and remodeling response to vascular injury.

4:15

803-2 Histological and Molecular Biological Characteristics of Restenotic Sapheneous Vein Grafts Post-Angioplasty

Sigrid Nikol[1,2], Peter Gonschior[1], Lawrence Weir[2], Jeffrey Isner[2], Berthold Höfling. [1] *Ludwig-Maximilians-Universität, München, Germany;* [2] *Tufts University, Boston, MA*

Vascular repair of vein grafts following angioplasty appears to be different from arterial vascular repair. This prompted us to investigate atherectomy specimens of patients who had undergone CABG surgery and underwent one or more angioplasties in a vein graft at the same site, for histology and TGF-β1 gene expression. 11 atherectomy specimens, 7 of patients with single and 4 of patients with multiple restenosis events were investigated. The mean time interval from the last restenosis event was 7.3 ± 5.2 months. Immunohistochemistry was performed using antibodies against α-actin, desmin, collagen I and IV, macrophages, monocyte-derived macrophages, endothelial structures and proliferation markers. *In situ* hybridization using a specific cDNA probe for TGF-β1 was performed and silver grains over nuclei and arbitrarily defined areas, indicating TGF-β1 expression, were counted. In adjacent sections cell density and areas containing extracellular neo-matrix were measured. Restenosis tissues compared with primary lesions showed a higher incidence of cellular components (70% vs 10%) and a lower macrophage content (20% vs 43%). Myocytes of varying phenotypes were seen in restenosis tissues, mainly meeting the criteria for "myofibroblasts". The area of extracellular neo-matrix correlated with the time interval of restenosis (r = 0.63), and both TGF-β1 expression and extracellular neo-matrix formation inversely correlated with cell density (r = 0.81 and r = 0.69, respectively). TGF-β1 expression was greater in lesions that had multiple restenotic events (15.1 ± 6.1 vs 5.6 ± 5.1 grains/nucleus, p < 0.05). *Conclusion:* Histological features of restenotic sapheneous vein grafts post-angioplasty are high cellularity, high "myofibroblast" and low macrophage

content. TGF-β1 gene expression is almost 3-fold increased in patients with multiple vs single restenosis events in sapheneous vein grafts. Overall, extracellular neo-matrix formation was continuously increased over time.

4:30

803-3 Influence of Presence or Absence of Medial Necrosis on Endothelial Regeneration and Intimal Hyperplasia in the Rabbit Carotid Artery

Frits N. Doornekamp, Mark J. Post, Cornelius Borst. *Heart Lung Institute, Utrecht University Hospital, Utrecht, The Netherlands*

Interventional injury induced intimal hyperplasia (IH) involves smooth muscle cell proliferation which may be limited by endothelial cell (EC) regeneration. We hypothesized that EC-regeneration (ECR) modulates IH. To create different ECR's we induced EC removal with 100% media necrosis (2F Fogarty balloon, 5 cm) and without media necrosis (prolene loop, 5 cm) in the rabbit carotid artery. After termination at 3, 7, 21 or 42 days, the artery was divided in segments which were alternately processed for paraffin- and frozen sections. ECR was assessed with an antibody to CD31 and expressed as percentage coverage. Proliferating cells were identified with an antibody to the nuclear antigen Ki-67 and scored as percentage positive cells. The cross-sectional IH area (IHA, mm^2) was measured morphometrically from elastin stained sections. *Results:* Wall coverage (%) with CD31 positive cells, IHA (mm^2) (mean ± sem, * = $p < 0.05$, † = $p < 0.001$, Fogarty balloon (BAL) versus loop):

	n	ECR,3d	ECR,7d	ECR,21d	ECR,42d	IHA,7d	IHA,21d	IHA,42d
BAL	7	3 ± 2	57 ± 14	61 ± 5	82 ± 11	0.01 ± 0.01	0.20 ± 0.01*	0.26 ± 0.03†
loop	7	8 ± 4	81 ± 10	93 ± 4	100 ± 0	0.01 ± 0.01	0.09 ± 0.04	0.08 ± 0.02

From 3–42 days, ECR was enhanced in loop versus balloon injured arteries ($P < 0.001$, ANOVA). At 3 and 7 days, more medial proliferation was found after balloon than after loop injury (3d: 46.2 ± 8.8% versus 0.2 ± 0.1%, 7d: 18.5 ± 6.4% versus 1.0 ± 0.4%; $p < 0.01$, ANOVA). In the same period, abundant adventitial proliferation was found after balloon injury which was entirely absent after loop injury.

Conclusion: Endothelial cell regeneration is slower over a damaged than over a normal media. This retarded endothelial cell regeneration may contribute to enhanced intimal hyperplasia.

4:45

803-4 Very Early Noninvasive Visualization of Experimental Atherosclerosis with Chimeric Antibody Z2D3 Radiolabeled with In-111 via Negatively-Charged Chelating Polymer, or Tc-99m via Glucarate Transchelation

Jagat Narula, Artiom Petrov, Charles Ditlow, Francis Chen, Chris Pak, Ban-An Khaw. *Northeastern University & Massachusetts General Hospital, Boston, MA; Scotgen Biopharmaceutical Inc., Menlo Park, CA*

We had reported the feasibility of noninvasive imaging of experimental atherosclerotic lesions with Indium-111-labeled mouse/human chimeric Z2D3 $F(ab')_2$ specific for proliferating smooth muscle cells in human atheroma. Lesions were visualized by 48 H. To reduce the delay between visualization and antibody administration, (i), Z2D3 $F(ab')_2$ was labeled with In-111 via negatively-charged chelating polymers (specific activity 500–1300 MBq/mg) and compared to the conventional In-111 labeled counterpart (specific activity 32–48 MBq/mg); and (ii), Z2D3 Fab' was labeled with Tc-99m via a weak transchelator, glucaric acid.

In vivo targeting was evaluated in 16 rabbits with atherosclerotic lesions induced by infradiaphragmatic balloon deendothelialization of the abdominal aorta followed by hyperlipidemic diet for 12 weeks. Four rabbits received 24 MBq (50 μg) of In-111-charge modified Z2D3 $F(ab')_2$. Two rabbits received 130 MBq (100 μg) of the kit formulation of this preparation. Six rabbits received 24 MBq (500–750 μg) of conventional Z2D3 $F(ab')_2$. The remaining 4 animals received Tc-99m Z2D3 Fab' (500–600 Mbq/375 μg). Gamma imaging revealed unequivocal tracer uptake in the abdominal atherosclerotic lesions at 24 H in all 4 animals injected with modified Z2D3. In 2 rabbits with higher specific radioactivity, the *lesions could be visualized at 3 H*. The blood pool activity in rabbits injected with the conventional Z2D3 did not permit definitive visualization of the lesions before 48 H. Blood clearance was significantly faster with modified Z2D3 (0.10 ± 0.008, Mean %ID/g ± SEM), as compared to the conventional Z2D3 (0.29 ± 0.04; $p < 0.01$). Uptake of modified Z2D3 preparations in atherosclerotic lesions at 24 H (0.08 ± 0.01) was similar to the conventional Z2D3 at 48 H (0.08 ± 0.02; p = NS). Tc-Fab' localization was visualizable at 12 H after administration of antibody. The Tc-Fab' uptake in the atherosclerotic lesion was significantly higher in the lesion (0.022 ± 0.004) compared to the normal (0.013 ± 0.002; $p = 0.04$) aorta. This study demonstrated the feasibility of very early noninvasive visualization of atherosclerotic lesions with antibody-based scintigraphy.

804 Treatment in Unstable Angina

Wednesday, March 22, 1995, 4:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, La Louisiane B

4:00

804-1 Heparin Pretreatment May Confer Additional Benefit in Patients Treated with 7E3 and PTCA for Unstable Coronary Syndromes

Mark C.G. Horrigan, David S. Eccleston, Nancy M. Wildermann, Kristina A. Sigmon, Robert M. Califf, Eric J. Topol, EPIC Investigators. *Cleveland Clinic Foundation, Cleveland, OH; Duke University Medical Center, Durham, NC*

Patients undergoing percutaneous intervention for unstable coronary syndromes associated with coronary thrombus are at substantially increased risk of ischemic complications. The incidence of ischemic complications in the EPIC trial was reduced in this subgroup (n = 893) by treatment with the chimeric monoclonal anti-IIb/IIIa antibody 7E3. We assessed the clinical effects of heparin pretreatment in this group. Data were available for 855 patients of whom 583 received 7E3 bolus or bolus and infusion. Of these, 383 (66%) were pretreated with heparin for a mean 55 hours [interquartile range 21, 96]. Outcomes examined included the primary 30 day composite endpoint (death, non-fatal infarction, CABG, repeat percutaneous intervention for acute ischemia) components thereof and major bleeding events.

	Pretreatment		
	Heparin (n = 383)	No heparin (n = 200)	Odds ratio (95% CI)
Primary endpoint	30 (7.8%)	25 (12.5%)	1.7 (0.9, 2.9)
Repeat percutaneous intervention or CABG	11 (2.9%)	10 (5.0%)	1.8 (0.7, 4.3)
Myocardial infarction	14 (3.7%)	13 (6.5%)	1.8 (0.8, 4.0)
Major bleeding event	20 (5.2%)	14 (7.0%)	1.3 (0.7, 2.8)

There was a strong trend toward further reduction of ischemic endpoints when patients received heparin pretreatment in addition to 7E3. This effect was not associated with an increased incidence of significant bleeding. These data support further investigation of the potentially additive roles of anti-platelet and anti-thrombotic treatments as adjuncts to percutaneous intervention in unstable coronary syndromes.

4:15

804-2 Low Molecular Weight Heparin, Regular Heparin or Aspirin to Treat Silent Ischemia in Unstable Angina

Enrique Gurfinkel, Ricardo Mejaíl, Eustaquio Manos, Miguel Cerdá, Ernesto Duronto, Claudio García, Ana Daroca, Branco Mautner. *Institute of Cardiology and Cardiovascular Surgery, Favaloro Foundation, Buenos Aires, Argentina*

We report a randomized prospective single blind study to test if low molecular weight heparin (LMWH) in a high dose (214 IC/kg anti-Xa, b.i.d.) by subcutaneous injection may achieve a potential benefit over regular heparin (RH) and or aspirin to reduce silent events and its complications. A total of 205 patients with angina at rest in the last 24 hrs before admission entered the study. Patients were monitored using a 2 channel device provided with an alarm signal system during the first 48 hrs and randomized to aspirin in a dose of 200 mg (Group A), aspirin plus RH (400 IU/kg/day i.v. trited by aPTT [Group B]) and aspirin plus LMWH (Group C). The end points were: (1) free of silent and symptomatic events; (2) recurrent angina, (3) AMI, (4) urgent intervention ([UI] PTCA or CABG), (5) major bleeding and (6) death. A total of 8234 hrs were recorded appropriately. Events rates were tested by two-tailed chi-square:

Groups		No Events		Recurrent Angina		AMI		UI	
G	n	n	p	n	p	n	p	n	p
A	69	28 (40%)	0.0002*	13 (19%)	0.1	4 (6%)	0.3	1 (1%)	0.6
B	69	27 (39%)	0.00001†	18 (26%)	0.01‡	1 (1%)		3 (4%)	
C	67	49 (73%)		6 (9%)		0		0	

*C vs A, †C vs B, ‡C vs B

Minor bleeding was detected in 10 cases in group B and 1 in C ($p = 0.006$). There was only 1 major bleeding in group B and no deaths in any group. *Conclusions:* In this study, treatment with LMWH in a high dose plus aspirin reached significantly better results than aspirin alone or aspirin plus RH.